Curr Cardiovasc Risk Rep (2015) 9: 37
DOI 10.1007/s12170-015-0465-2

Dipeptidyl Peptidase-4 Inhibitors and Heart Failure: Friends or Foes?

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Published online: 29 May 2015

Abstract Heart failure (HF) is one of the leading causes of morbidity and mortality. Several risk factors have been identified that have been consistently associated with the development of HF, including type 2 diabetes and glucose-lowering agents. However, different drugs for type 2 diabetes may have diverse, and even divergent, effects on heart failure. The insulin-sensitizing thiazolidinediones have been associated with increased rates of HF in randomized controlled trials, whereas for other drugs, this relationship is less clear. Before the publication of the SAVOR-TIMI53 trial, available data suggested that DPP4 inhibitors could have a protective effect with respect to incident HF. The possibility of a causal finding cannot be ruled out, but it appears rather unlikely, considering that another cardiovascular outcome study showed a trend toward an increased risk with a different molecule of the same class, and that some epidemiological studies associated sitagliptin to an increased risk of HF. This review explores the possible mechanisms underlying the association of DPP4 inhibitor use with an increased risk for incident HF.

Keywords Heart failure · Diabetes · Glucose-lowering agents · DPP-4 inhibitors

This article is part of the Topical Collection on *Diabetes + Insulin Resistance*

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Introduction

"Heart failure (HF) is one of the leading causes of morbidity and mortality [1•, 2•] and its prevalence continues to rise in the U.S. [3•], despite the decline in cardiovascular death rates [4•]. Several risk factors have been identified as consistently associated with the development" of HF, including age, male gender, left ventricular hypertrophy, diabetes mellitus, valvular heart disease, hypertension, myocardial infarction, left ventricular dysfunction, and obesity. Type 2 diabetes is one of the most important predictors of incident HF, as observed in several epidemiological studies [5•].

The mechanisms leading to the greater rates of HF in type 2 "diabetic patients are likely multifactorial and include the shared and accelerated comorbid conditions of hypertension, coronary artery disease, obesity, renal insufficiency, and aortic stiffness. In addition, insulin resistance and hyperglycemia may contribute directly to cardiac dysfunction through mechanisms related to the direct and indirect effects of advanced glycation" endproducts, abnormalities of cardiac metabolism, myocardiocyte autophagy, increased myocardial fibrosis, oxidative stress, and local activation of the renin-angiotensin system [6]. "Increasing evidence also suggests that HF itself may be considered an insulin resistant state with increased risk for the development of diabetes in patients with established HF" [7]. Clinical predictors of incident diabetes in HF patients include obesity, higher glucose levels, diuretic therapy, digoxin therapy, lower serum creatinine concentration, and more severe NYHA class [6, 8–11].

Given this interrelationship between diabetes and HF, it is not surprising that these conditions often coexist in the same individuals. In studies of patients with left ventricular dysfunction, it is estimated that approximately 12–30 % of individuals have known diabetes [12]. The prevalence may be even greater when more systematic screening for diabetes is

performed in HF populations. "In a cohort of outpatients with systolic HF who underwent oral glucose tolerance testing, 18 % of individuals" showed a previously undiagnosed diabetes [13]. Importantly, the coexistence of diabetes and HF portends a poor prognosis. Population studies [14] and clinical trials [15–17] have demonstrated that diabetes is associated with increased mortality in HF patients. This diabetes-associated increased risk of death persists after adjustment for clinically recognized potential confounders. Similarly, recurrent hospitalizations for HF are markedly increased in individuals with diabetes. In the CHARM study, performed in patients with chronic HF, rates of HF hospitalization in patients with diabetes were also approximately twice the rates of those without diabetes [11]. Given the health burden of diabetes in HF patients, "it is important to understand the balance that exists between the treatments of both conditions. Specifically, pharmacologic therapies that are used to treat HF may affect glycemic levels and the future risk" of diabetes (see below). "Similarly, it is important to understand the potential role and challenges in commonly used glycemic therapies that may be particularly relevant in HF patients" or in patients at high risk for developing HF (see below).

Drugs for Heart Failure and Diabetes

Beta-blockers have been associated with a worsened glycemic control due to a negative effect on insulin secretion [18]. In addition, those drugs are sometimes avoided in patients treated with insulin or insulin secretagogues for a theoretical risk of hypoglycemia unawareness. On the other hand, several studies have shown a number of beneficial effects of this class of drugs in patients with diabetes and HF [19, 20]. In a meta-analysis of randomized controlled trials, beta-blockers reduced mortality by about 15 % in diabetic patients with HF [19]. The effects of beta-blockers on HF in patients with diabetes are similar to those observed in those without diabetes [21–23].

"Randomized clinical trials have clearly established improved survival with the use of angiotensin-converting enzyme inhibitors" (ACEI) in diabetic patients with HF [21]. "In addition to beneficial effects on clinical outcomes, some studies have demonstrated associations between" ACEI or ARBs and reduced incidence of new diabetes in HF patients. Data from the Studies of Left Ventricular Dysfunction (SOLVD [24]) and the CHARM Program [25] have demonstrated reduced incidence of new diabetes in patients treated with enalapril and candesartan, respectively, when compared with placebo. There are some available data showing that the inhibition of the renin-angiotensin system could be associated with a mild improvement of insulin sensitivity [26].

Aliskiren is a first-in-class direct renin inhibitor. Efficacy and safety of aliskiren in patients with type 2 diabetes and proteinuria or ischemic heart disease were assessed in the ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints) study [27], which was prematurely terminated due to an increased risk of renal dysfunction and stroke. The results of the ASTRONAUT trial, which enrolled patients admitted to the hospital for HF [28], are not yet available.

The unfavorable effects of diuretic therapy (both thiazide and loop diuretics) on insulin sensitivity and glycemic control have been extensively investigated [29–31]. However, in most instances, diuretics are inevitable in the treatment of patients with HF.

Glucose-lowering Agents and Heart Failure

Different drugs for type 2 diabetes may have diverse, and even divergent, effects on heart failure.

The insulin-sensitizing thiazolidinediones (TZDs) have been associated with increased rates of HF in randomized controlled trials [32–34]. This effect is entirely determined by fluid retention since TZDs have no direct detrimental effect on cardiac function. For this reason, TZDs are contraindicated in patients with HF irrespective of their NYHA class.

Sulfonylureas are frequently used in diabetic patients with HF. In a study of more than 16,000 "Medicare recipients who had been discharged with a diagnosis of HF, approximately half of the patients were treated with sulfonylureas" [35]. In that observational study, sulfonylurea was not associated with increased mortality (hazard ratio [HR] 0.99; 95 CI 0.91–1.08) [35]. However, sulfonylureas are associated with hypoglycemia and weight gain, and these side effects could theoretically worsen the prognosis of ischemic heart disease and HF [36, 37]. In addition, experimental studies have shown that sulfonylureas may have proarrhythmic effects [38, 39], reduce resting myocardial blood flow [40], and increase anatomical and functional damage after myocardial ischemia [41, 42]. Sulfonylureas bind to a myocardial ATP-dependent K channel, reducing potassium currents during ischemia; this leads to impaired adaptation of myocardiocytes to ischemic conditions. In an animal model of ischemia/reperfusion injury, the administration of sulfonylureas is associated to increased infarct size and reduced left ventricular function [42]. In patients with type 2 diabetes and myocardial ischemia, sulfonylureas reduce cardiac function in comparison with insulin [43]. These data suggest caution in the use of sulfonylureas in patients with HF.

Metformin is currently recommended as first-line therapy in patients with type 2 diabetes. Metformin is contraindicated in individuals with severe HF (NYHA class III–IV), due to concerns of lactic acidosis [44]. However, recent observational studies have suggested that metformin is not only safe, but it could be also associated with improved survival in patients with diabetes and chronic HF [35]. A possible detrimental effect of metformin is represented by the impairment of intestinal absorption of B vitamins and folate [45]. In fact, this

deficiency could cause an increase of homocysteine plasma levels, possibly affecting platelet and endothelium function. Some evidence suggests a direct association between homocysteine plasma levels and all-cause mortality in patients with ischemic heart disease [46].

Many patients with diabetes and HF require insulin, either as monotherapy or in combination with other glucose-lowering agents. The evidence regarding the effect of insulin on mortality in HF is conflicting, and no large randomized controlled trials have been performed in these patients. However, insulin can cause fluid retention, particularly when administered at high doses, potentially increasing the risk of incident HF or worsening a preexisting HF. In the CHARM study, for example, type 2 diabetic patients with HF treated with insulin had a greater risk of all-cause death, than those treated with other glucose-lowering agents [16]. These results were not confirmed in other studies in which, insulin use was not associated with an increased risk of mortality [35]. However, observational data deserve a cautious interpretation since insulin can be a marker of severity of diabetes and HF.

DPP4 Inhibitors and Heart Failure: The Expectations

Before the publication of the SAVOR-TIMI53 trial in 2013 [47•], available data suggested that DPP4 inhibitors could have a protective effect with respect to heart failure. Besides the potential benefit derived from the improvement of glycemic control, DPP4 inhibitors appeared to have favorable effects on cardiovascular risk factors other than blood glucose. Despite some experimental data suggesting that inhibition of DPP4 could induce dyslipidemia through the modulation of steroid metabolism [48], clinical trials showed a small but significant improvement in cholesterol and triglyceride levels [49]. These data deserve a cautious interpretation because many trials do not report the effects on lipids, suggesting the possibility of a publication bias in favor of positive results. Although the reduction of triglyceride could be partly due to the improvement of glucose control, a direct inhibition of hepatic lipogenesis by GLP-1 has also been experimentally demonstrated [50]. On the other hand, the actions of DPP4 inhibitors on blood pressure are controversial. While GLP-1 receptor agonists reduce blood pressure and increase heart rate [51, 52], no such effect is observed with DPP4 inhibitors. In animal studies, the inhibition of DPP4 can either increase or reduce blood pressure, depending on the experimental model [53]. GLP-1 could reduce blood pressure by stimulating nitric oxide release and endothelium-dependent vasodilation [54, 55], but it could also have vasoconstrictor effects in some conditions [53]. In addition, other substrates of DPP4 (e.g., neuropeptide Y) modulate vascular tone [53].

Overall, the effect of DPP4 inhibitors on cardiovascular risk appears to be favorable. Early trials designed for metabolic outcomes confirmed these expectations, showing a significant reduction of cardiovascular morbidity and all-cause mortality versus comparator arms [56, 57]. A reduction in the incidence of ischemic heart disease should theoretically produce a comparable decrease in the risk of heart failure.

Early expectations of a relevant reduction of cardiovascular morbidity with DPP4 inhibitors were not confirmed by specifically designed cardiovascular outcome trials performed in patients at higher cardiovascular risk [47•, 58•]. However, there were other reasons to believe that DPP4 inhibitors could prevent heart failure, even in patients already affected by ischemic heart disease. GLP-1 receptors are expressed in the myocardium, and they appear to have a physiologic role in the regulation of cardiac function. GLP-1 receptor knockout mice exhibit elevated left ventricular end-diastolic pressure, increased leftventricular thickness and reduced resting heart rate compared with wild-type control animals [59]. Continuous GLP-1 infusion ameliorates left ventricular dysfunction in animal models of dilated cardiomyopathy [60] and in patients affected by chronic heart failure, irrespective of diabetes [61]. Taken together, these data suggest that GLP-1, which is increased by treatment with DPP4 inhibitors, stimulates cardiac function. In addition, the active form of GLP-1 could protect the heart from ischemic damage. In rodents, the administration of GLP-1 enhances pre-ischemic conditioning and limits infarct size [62, 63]. Moreover, a 72-h continuous intravenous infusion of GLP-1 improves functional myocardial recovery in predominantly nondiabetic humans with acute myocardial infarction and successful reperfusion [64]. GLP-1 could provide protection from ischemia through the inhibition of some proapoptotic pathways, possibly via the activation of ERK and PI-3kinase [62, 65].

Experimental and clinical data on the cardiac effects of GLP-1 are usually observed with supraphysiological concentrations of the hormone, which are much higher than those reached with DPP4 inhibitors. However, some data suggest that even the moderate increase in GLP-1 obtained with the inhibition of DPP4 could have some direct myocardial effects. In DPP4 knockout mice, survival and recovery after experimental myocardial infarction are improved in comparison to wild-type animals [66]. Treatment with sitagliptin reduces infarct size and improves recovery after ischemia reperfusion in mice [66, 67]; vildagliptin did not confer protection from ischemia in rats [68], but it improved cardiac function in pressure-overloaded mice [69]. In humans, in a pilot trial in patients with coronary artery disease, a single dose of sitagliptin ameliorated left ventricular dysfunction during dobutamine-induced ischemia [70].

Taken together, all the available experimental and clinical evidence in 2013 suggested that treatment with DPP4 inhibitors could be effective in preventing HF in patients with diabetes—or at least that it could be safe in this respect.

DPP4 Inhibitors and Heart Failure: The Evidence

The finding of a 26 % increase in the risk of hospitalization for HF with saxagliptin, compared to placebo, in the SAVOR-TIMI53 study [47•] was totally unexpected. Notably, the excess risk occurred only during the first 12 months of treatment, and there was no increase neither in the incidence of new cases of HF nor in mortality for HF [47•]. This result could be interpreted as a casual finding: when exploring many endpoints, a statistically significant difference can be the effect of chance. However, the possibility of a real detrimental effect on HF of saxagliptin, or of the whole class of DPP4 inhibitors, deserves full consideration.

Hospitalization for HF was not among predefined endpoints of the EXAMINE trial, the placebo-controlled, cardiovascular outcome study with alogliptin. A post hoc analysis revealed a relative risk of 1.19, which did not reach statistical significance; however, the overall number of cases of hospitalization for HR (and therefore the statistical power) was smaller than that of SAVOR-TIMI53 [58•]. Although nonsignificant findings are always difficult to interpret, a trend toward an increased risk for HF can be observed also for alogliptin, which has a chemical structure quite different from that of saxagliptin, despite a similar pharmacological activity.

Overall, combining all results of available trials in a meta-analysis, DPP4 inhibitors as a class appear to be associated with an increased risk of HF [71•]. Nonetheless, the result of the meta-analysis is largely driven by the two cardiovascular outcome trials, SAVOR-TIMI53 and EXAMINE. Earlier studies with metabolic endpoints, in which cases of HF had been recorded as treatment-emergent serious adverse events, had not revealed any signal of risk, although the number of events in those studies had been quite small [71•].

Further data are needed to establish more clearly if the increase in the hospitalizations for HF is a class effect. A smaller 52-week study with vildagliptin in patients with congestive heart failure, with left ventricular function as the primary endpoint, has been recently completed (https://www.clinicaltrial.gov/ct2/show/NCT00894868), but the results have not been published in full so far. In addition, another cardiovascular outcome study with a DPP4 inhibitor, the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), will be soon available [72, 73]. Those trials will certainly add further insight.

For the moment, some additional information can be obtained by observational studies. In a cohort of Taiwanese patients treated with sitagliptin, the incidence of hospitalization for HF over a mean of 1.5 years of follow-up was increased by 20 % over a control-matched cohort [74]. A significant increase in risk associated with sitagliptin was also reported in a US population-based cohort of diabetic patients with known HF [75]. The results of epidemiological (i.e., observational) studies maybe affected by prescription bias since some of the alternative drugs, such as thiazolidinediones or sulfonylureas, have been associated with increased risk of cardiac dysfunction or heart failure, the chance of receiving a prescription of a DPP4 inhibitor could have been greater in patients at higher risk of severe HF. On the other hand, since DPP4 inhibitors are associated with reduced overall cardiovascular morbidity and mortality in epidemiological studies [76], the hypothesis of an overprescription in patients at higher cardiovascular risk does not seem very plausible. This bias is reduced, but not necessarily eliminated, when multiple confounders are considered in study design and statistical analysis. On the other hand, the results of epidemiological studies to date appear to be concordant with those of cardiovascular outcome trials with DPP4 inhibitors, supporting the hypothesis of a class effect on HF risk.

The fact that a possible increase in risk was not detected earlier trials with metabolic outcomes may seem surprising. The number of cases of HF reported as serious adverse events in early trials with DPP4 inhibitors was very small; differences in risk between treatment arms could have remained unnoticed because of insufficient statistical power [71•]. It is also possible that the increase in risk is evident only in cardiovascular outcome trials, which enroll patients with different characteristics from those of earlier studies. Both the EXAMINE and the SAVOR-TIMI53 trials enrolled patients with high cardiovascular risk [47•, 58•], who, when compared to those of early trials, had a higher age; a longer duration of diabetes; a higher prevalence of prior cardiovascular disease; established heart failure, renal failure, and other comorbidities; and were more frequently treated with insulin. It is theoretically possible that any one of those characteristics modulates DPP4 inhibitor-associated risk of hospitalization for heart failure.

A number of post hoc analyses have been performed on the results of the SAVOR-TIMI53 trial in order to identify subgroups with a greater susceptibility to saxagliptin-induced hospitalization for HF. The authors failed to identify any significant predictors; in particular, previous HF, renal insufficiency, insulin therapy, age, gender, and duration of diabetes all failed to predict the effect of saxagliptin on incident hospitalizations for HF [47•]. In a subgroup of patients, baseline determinations of pre-proBNP were also available; however, the relative risk of hospitalization for HF associated with saxagliptin in the highest quartile of pre-proBNP was similar to that observed in the rest of the sample [47•]. It should be considered that the number of events of hospitalization for HF in the SAVOR-TIMI53 trial was rather small, and that it could have been insufficient to detect relevant predictors.

DPP4 Inhibitors and HF: The Mechanisms

The possible mechanisms underlying the association of DPP4i with HF remain elusive (Fig. 1).

The wide distribution of DPPIV in different tissues, including heart, kidney, and endothelium, and its capability of

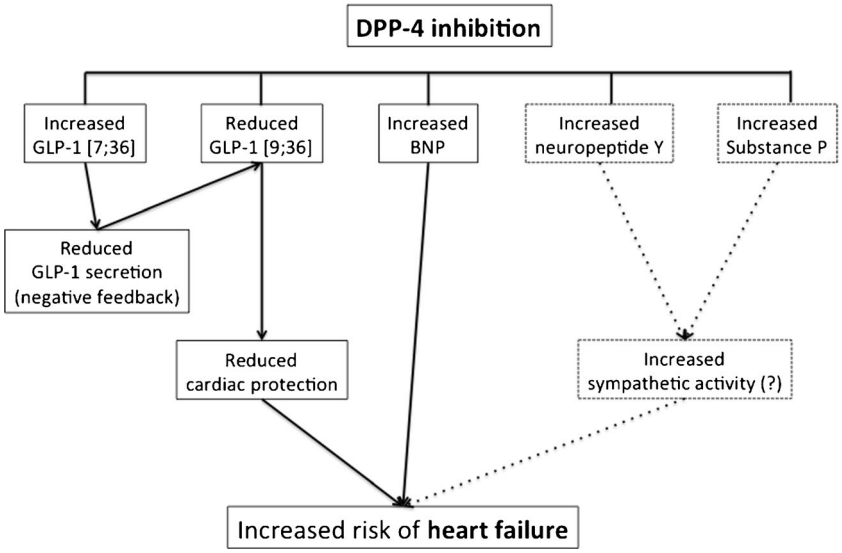

Fig. 1 Possible mechanisms underlying the association of DPP4 inhibitors with heart failure

inactivating not only GLP-1 but also brain natriuretic peptide (BNP; [78]) and other vasoactive peptides [77], suggests a potential role for this peptidase in the pathophysiology of cardiovascular diseases. It has been demonstrated that myocardiocytes of rats with experimental HF show a higher DPP4 expression and activity; this phenomenon could suggest either a direct effect of this peptidase in the pathogenesis of cardiac dysfunction or its activation as a compensatory mechanism. Higher circulating DPP4 activity appears to be correlated with poorer outcomes of HF in both rodents and humans [78], whereas DPP4 knockout animals show an improved recovery after myocardial infarction [66]. In animal models, the administration of DPP4 inhibitors significantly attenuates HF-related cardiac remodeling and dysfunction and reduces infarct size after experimental ischemia and reperfusion [66, 67, 69]. This cardio-protective effect, which could be attributed, at least partly, to increased GLP-1 bioavailability and stimulation of the cardiac receptor for GLP-1, is consistent with the results obtained in humans in short-term studies [70].

On the other hand, it is possible that prolonged inhibition of DPP4 leads to a decrease in ventricular function. In the SAVOR-TIMI53 study, the increase in risk of hospitalization for HF was not associated with a higher incidence of edema or to weight gain; this suggests that the effect may be due to depressed myocardial function, rather than to fluid retention [47•]. At the same time, potential mechanisms accounting for a reduction of cardiac function as a consequence of DPP4 inhibition are speculative.

One possible mechanism is the reduction of circulating GLP-1[9-36] levels during treatment with DPP-4 inhibitors. The active form of GLP-1 is GLP1[7-36], whereas intact GLP1[1-36] is biologically inactive precursor. GLP1[9-36] is the "inactivated" form of the hormone, and it is the product of the action of DPP4 on active GLP1 (i.e., GLP1[7-36]). Since GLP1[7-36] inhibits its own secretion with a negative feedback, its increase determined by DPP4 inhibition determines a reduction of total GLP1 secretion and therefore of circulating GLP1[9-36] levels [79]. GLP-1[9-36] has long been considered inactive since its affinity for GLP1 receptors is minimal; however, experiments in animal models have shown that "inactive" GLP1 mimics some of the stimulatory effects of active GLP1 on myocardial function, possibly via a GLP1 receptor-independent pathway [80]. DPP4 inhibitors could interfere with cardiac function by reducing the positive myocardial actions of GLP1[9-36]. However, these latter effects of inactive GLP1 have been observed in rodents but never confirmed in humans so far.

Several other molecules, including some vasoactive peptides, are substrates of DPP4. Brain natriuretic peptide (BNP), whose plasma levels positively correlate with the degree of left ventricular dysfunction [81], is inactivated by DPP4 and therefore increases during treatment with DPP4 inhibitors. However, the increase of BNP is considered a compensatory mechanism, rather than a pathogenic mechanism, for HF. DPP4 also mediates the cleavage of neuropeptide Y (NPY) and peptide YY (PYY) to inactivated forms. "Notably, NPY levels have been found to be elevated in HF patients and to correlate with tachycardia and left-sided HF" [82]. Moreover, recent studies have shown that substance P (also inactivated by DPP4) and NPY (both increased during treatment with DPP4 inhibitors) stimulate sympathetic activity when angiotensin-converting enzyme inhibitors are co-administered to DPP4 inhibitors [83].

The possibility that some or all DPP4 inhibitors have a pharmacokinetic or pharmacodynamic interaction with cardiovascular drugs used in patients with HF should be carefully considered. Although post hoc analyses of the SAVOR-TIMI53 study failed to show any significant effect of co-administration of any drug on saxagliptin-induced risk for hospitalization for heart failure, the number of events could have been insufficient to highlight such associations.

Conclusions

Large-scale clinical trials can produce unexpected results. This is the case of the increase in the risk of hospitalization for HF observed with saxagliptin in the SAVOR-TIMI53 study [47•]. The possibility of a causal finding cannot be ruled out, but it appears rather unlikely, considering that another cardiovascular outcome study showed a trend toward an increased risk with a different molecule of the same class [58•], and that some epidemiological studies associated a third agent of the class to an increased risk of HF [74, 75]. Although a negative effect of DPP4 inhibition on cardiac function was unexpected, there are several hypothetical mechanisms through which DPP4 inhibitors could exacerbate HF. At the same time, presently available experimental and clinical data are insufficient to provide a clear picture of causal relationships between DPP4 inhibition and signs and symptoms of HF. It is important to remember that the increase in risk for hospitalization for HF is mild to moderate that it is not associated to any detrimental effect on all-cause or cause-specific mortality and that the overall incidence of major cardiovascular events is not increased, and it may even be reduced by DPP4 inhibitors. This unexpected adverse event does not seem to affect in a relevant manner the risk-benefit ratio of this class of drugs. From a clinical standpoint, there is no possibility to identify patients at a higher risk for DPP4 inhibitor-induced HF. Therefore, it could be advisable to check for symptoms of HF in patients with cardiac dysfunction shortly after the initiation of treatment with DPP4 inhibitors.

Compliance with Ethics Guidelines

Conflict of Interest Edoardo Mannucci received speaking honoraria, consultancy fee, and/or research grants from AstraZeneca, Boehringer Ingelheim, Merck, Novartis, and Takeda. Matteo Monami reports personal fees from AstraZeneca, personal fees from Boehringer, personal fees from Eli Lilly, personal fees from Novo Nordisk, personal fees from Sanofi, personal fees from Takeda, personal fees from BMS, and personal fees from Merck outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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